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## (54) Tablets comprising a combination of metformin and glibenclamide

(57) The present invention relates to a tablet comprising a combination of metformin and glibenclamide in which the size of the glibenclamide is such that at most 10% of the particles are less than 2 μm and at most 10% of the particles are greater than 60 μm.

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## Description

[0001] The present invention relates to tablets for the treatment of non-insulin dependent diabetes.

[0002] Non-insulin dependent diabetes is a metabolic disorder characterized by hyperglycaemia, which occurs due to insulin deficiency, insulin resistance and reduced glucose tolerance.

[0003] There are two main groups of oral antidiabetic drugs available: these are the sulphonylureas and the biguanidines. Sulphonylureas act by stimulating insulin release and are thus only effective with some residual pancreatic beta-cell activity, examples of sulphonylureas available are glibenclamide, gliclazide, tolbutamide, glipizide, tolazamide, gliquidone and chlorpropamide. The biguanidines, such as metformin, act by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose, and as they require endogenous insulin they are only effective with some residual pancreatic islet cell activity.

[0004] The initial treatment of non-insulin dependent diabetes involves diet control and exercise. Only after this has been shown to be inadequate are oral antidiabetic drugs used, and then only to complement the effect of diet and not replace it. Monotherapy with an oral antidiabetic can be an effective treatment for many years. However the efficiency can decrease with time. Due to sulphonylureas and biguanidines having complementary modes of action, combined therapy is now an established form of treatment for non-insulin dependent diabetes.

[0005] As treatment of non-insulin dependent diabetes is control rather than cure patient compliance is critical. Thus to improve patient compliance a combined tablet would be an advantage. The present invention relates to tablets comprising a combination of metformin and glibenclamide.

[0006] It is possible to be produce a combination tablet using standard galenic procedures. However, when using standard generic glibenclamide in the combination tablet a reduced bioavailability in comparison to the co-prescribed situation was apparent. It has been found using in-vitro and in-vivo testing that the reduced bioavailability is related to the particle size and the particle size distribution of the glibenclamide. It has been found that particles which are too small result in high glibenclamide blood levels with consequent risk of hypoglycaemia and particles which are too large cannot dissolve sufficiently rapidly from the metformin tablet matrix to give comparable bioavailability with the co-prescribed situation. It is therefore necessary to have a closely defined particle size distribution of the glibenclamide in the combination tablet.

[0007] The selection of a specific size fraction of glibenclamide enables the production of a combination tablet exhibiting comparable glibenclamide bioavailability to the co-administered tablets, when judged by the area under the curve of the in-vivo analysis.

[0008] The present invention provides a tablet comprising a combination of metformin and glibenclamide, exhibiting a comparable glibenclamide bioavailability to the co-administered tablets.

[0009] The tablet according to the invention contains a combination of glibenclamide and metformin in which the size of the glibenclamide is such that at most 10% of the particles are less than 2 μm and at most 10% of the particles are greater than 60 μm. Preferably, the size of the glibenclamide is such that at most 10% of the particles are less than 3 μm and at most 10% of the particles are greater than 40 μm. This specific particle size range of glibenclamide may be obtained by sieving or air jet milling.

[0010] Metformin may be used as a salt of metformin, such as hydrochloride fumarate, hydrobromide, p-chlorophenoxy acetate or embonate. The weight ratio of metformin salt to glibenclamide should preferably be between 50/1 to 250/1.

[0011] The tablet according to the present invention may be obtained by a process comprising:

a) forming granules by wet granulation of a mixture of metformin and glibenclamide;
b) blending the granules with a tabletting aid and diluent, and
c) tabletting the blend thus obtained into tablets.

[0012] Advantageously the mixture used for forming the granules comprises a granulating binder. This granulating binder is in particular a polyvinylpyrolidone such as for example, a polyvinylpyrolidone having a molecular weight of 45 000. The polyvinylpyrolidone may be used in a proportion of 2 to 4% by weight with respect to the final tablet.

[0013] After the granulating step the granules may be sieved and dried.

[0014] The granules are then blended with a diluent and tabletting aid. The diluent may be any material usually used for making tablets, such as microcrystaline cellulose. The tabletting aid may be any material usually for making tablets, such as magnesium stearate.

[0015] The tablets thus obtained may then be coated with a hydrophilic cellulose polymer and talc. The hydrophilic cellulose polymer may be 2-hydroxypropyl methylcellulose.

[0016] The following examples illustrate the process for the preparation of the tablets.

Example 1

[0017] A tablet of metformin/glibenclamide has been prepared as follows:

[0018] 66.6 g of polyvinylpyrolidone are mixed with 246 g of purified water with a stirrer. 1500 g metformin hydrochloride, 7.5 g of glibenclamide (with a 10 to 90% size range between 2 to 60 μm), 42 g croscarmellose sodium and 284.4 g of microcrystalline cellulose are

mixed in a granulator. The polyvinylpyronolidone solution is added to the granulator and the wet mass is granulated. The granules are extruded through a 1 mm mesh. The granules are emptied into a preheated fluidised bed dryer and the granules are dried. 97.5 g of microcrystalline cellulose is mixed into the granules using a tumbling mixer. 12 g of magnesium stearate is added to the tumbling mixer and mix. The granule mix is tabletted using a suitable tablet press. The tablets are coated with a 2% hydroxypropyl methylcellulose coat in a coating machine.

Example 2

**[0019]** A tablet of metformin/glibenclamide has been prepared as follows:

**[0020]** 5.83 g of glibenclamide (with a 10 to 90% size range between 2 to 60 μm), are preblended with 32.67 g of croscarmellose sodium. 46.67 g of polyvinylpyrolidone are mixed with 93.33 g of purified water with a stirrer. The glibenclamide-croscarmellose sodium blend is mixed with 1166.6 g of metformin hydrochloride in a granulator. The polyvinylpyrolidone solution is added to the granulator and the wet mass is granulated. The granules are emptied into a preheated fluidised bed dryer and the granules are dried. The particle size of the granules is reduced by passing through a 1 mm mesh. 131.83 g of microcrystalline celulose are mixed into the granules in the granulator 16.3 g of magnesium stearate are added to the granulator and mixed. The granule mix is tabletted using a suitable tablet press. The tablets are coated with a 2% hydroxypropyl methylcellulose coat in a coating machine.

**[0021]** In-vivo bioavailability tests were performed with tablets prepared as disclosed in example 2, using two batches of glibenclamide. The two batches have the following 10 to 90% particle size range:

batch A: 3.47-38.08 μm
batch B: 15.63-91.6 μm.

**[0022]** The distribution of the particle size of batches A and B are illustrated in figure 1.

**[0023]** The two batches of tablets were administered to healthy patients in comparison to co-administered glibenclamide (marketed under the trade name Daonil) and metformin hydrochloride (16 patients for each group).

**[0024]** The comparative concentrations of glibenclamide in a tablet comprising a combination of metformin and respectively the batch A and the batch B of glibenclamide and with the co-administration are shown respectively in figures 2 and 3.

**[0025]** The area under the curve (AUC) are the following:

| | AUC (ng/ml/h) |
|---|---|
| combination with batch A | 790.5 |
| combination with batch B | 353.0 |
| co-administration | 869.3 |

**[0026]** It appears that with the combination according to the invention with batch A the AUC is substancially the same as in the case of co-administration, whereas with the combination with batch B the AUC is more clearly different.

**Claims**

1. A tablet comprising a combination of metformin and glibenclamide in which the size of the glibenclamide is such that at most 10% of the particles are less than 2 μm and at most 10% of the particles are greater than 60 μm.

2. A tablet as claimed in claim 1 in which the size of the glibenclamide is such that at most 10% of the particles are less than 3 μm at most 10% of the particles are greater than 40 μm.

3. A tablet as claimed in claim 1 or 2 in which metformin is present as metformin salt and the weight ratio of metformin salt to glibenclamide is 50/1 to 250/1.

4. A tablet as claimed in anyone of claims 1 to 3 which is obtained by a process comprising:

   a) forming granules by wet granulation of a mixture of metformin and glibenclamide;
   b) blending the granules with a tabletting aid
   c) tabletting the blend thus obtained into tablets.

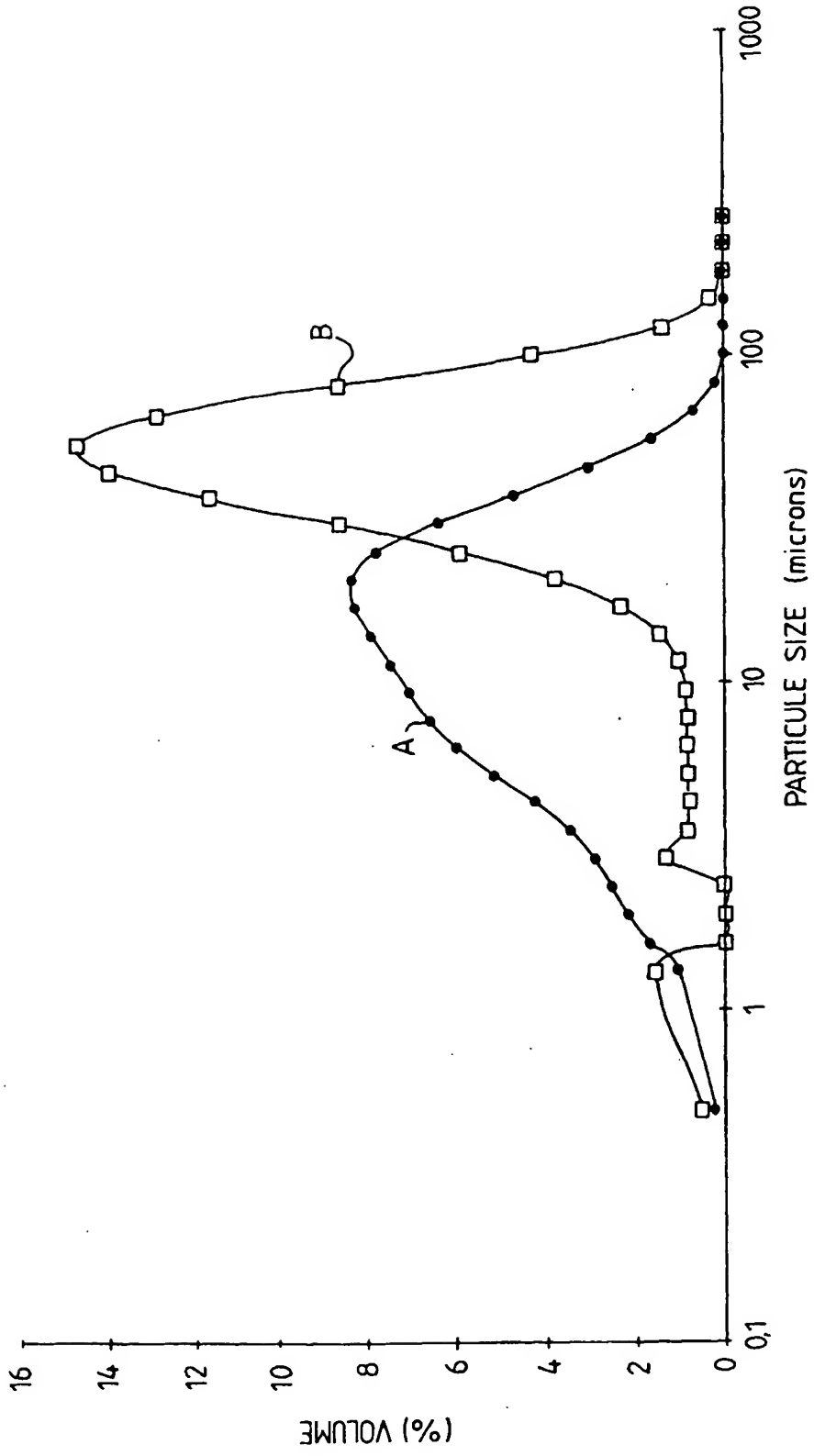
VOLUME (%)
16
14
12
10
8
6
4
2
0
0,1
1
10
100
1000
PARTICULE SIZE (microns)
A
B

FIG.1

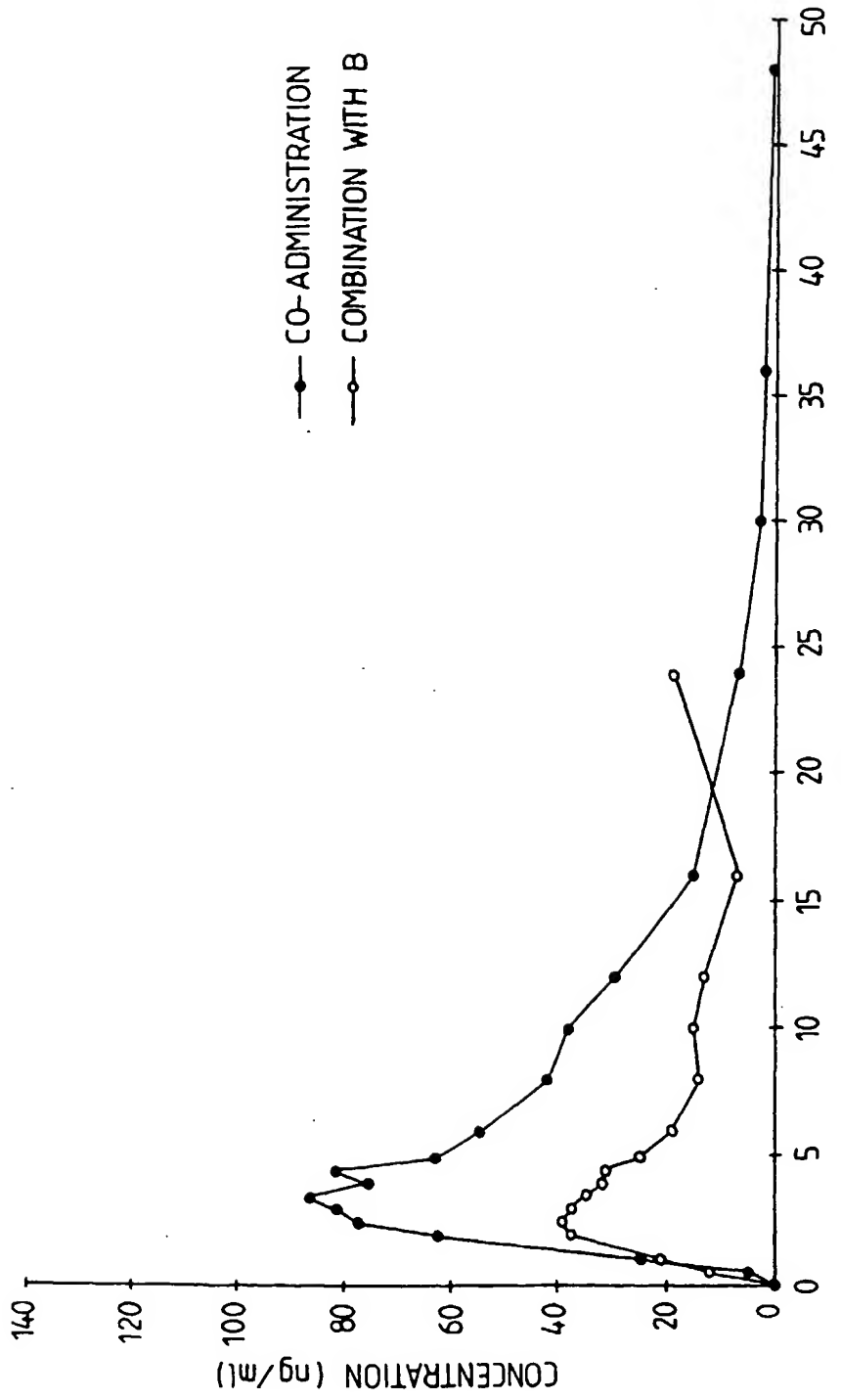
CO-ADMINISTRATION
COMBINATION WITH B
CONCENTRATION (ng/ml)
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
50
TIME (hours)

FIG. 2

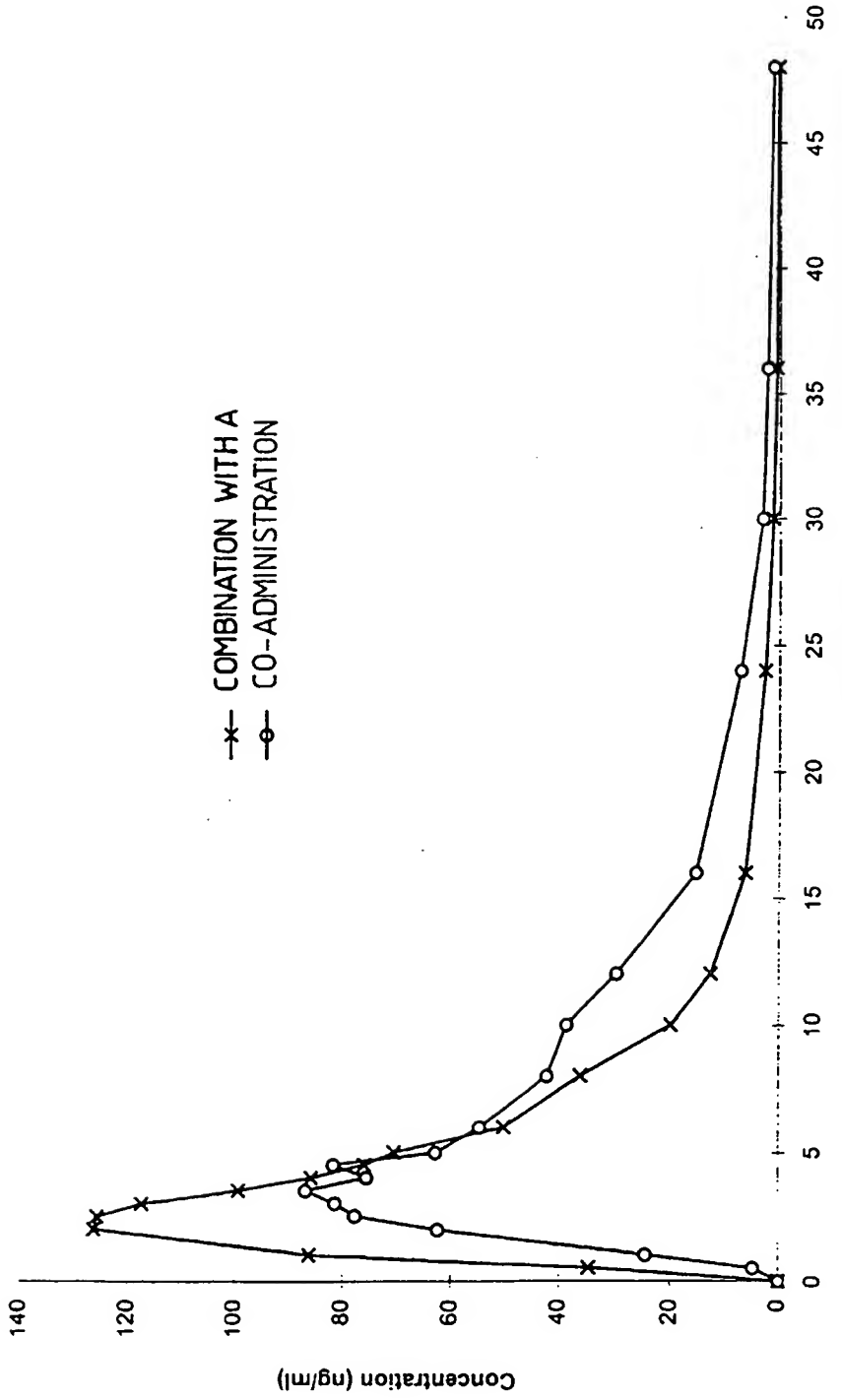
COMBINATION WITH A
CO-ADMINISTRATION
Concentration (ng/ml)
Time (hours)
0
20
40
60
80
100
120
140
0
5
10
15
20
25
30
35
40
45
50

FIG. 3

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# EUROPEAN SEARCH REPORT

Application Number
EP 98 40 1781

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
|---|---|---|---|
| Y | WO 97 17975 A (GENTILI IST SPA ;BARELLI GIULIO (IT); REGIS MASSIMO DE (IT)) 22 May 1997 * claims * | 1-4 | A61K31/64 //(A61K31/64, 31:155) |
| Y | US 4 060 634 A (ROTHE WERNER ET AL) 29 November 1977 * column 4, line 32 - line 49 * | 1-4 | |
| | | | TECHNICAL FIELDS SEARCHED (Int.Cl.6) |
| | | | A61K |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 14 January 1999 | Leherte, C |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

## ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 98 40 1781

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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14-01-1999

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9717975 A | 22-05-1997 | IT MI952337 A | 14-05-1997 |
| | | AU 7566896 A | 05-06-1997 |
| | | CA 2237571 A | 22-05-1997 |
| | | EP 0869796 A | 14-10-1998 |
| US 4060634 A | 29-11-1977 | DE 2348334 A | 27-03-1975 |
| | | AT 330954 B | 26-07-1976 |
| | | AT 762374 A | 15-10-1975 |
| | | AU 7365374 A | 01-04-1976 |
| | | BE 820254 A | 24-03-1975 |
| | | CA 1029661 A | 18-04-1978 |
| | | FI 275574 A,B, | 27-03-1975 |
| | | FR 2244455 A | 18-04-1975 |
| | | GB 1420907 A | 14-01-1976 |
| | | JP 1089246 C | 23-03-1982 |
| | | JP 50058216 A | 21-05-1975 |
| | | JP 56032967 B | 31-07-1981 |
| | | NL 7412393 A,B, | 01-04-1975 |
| | | SE 402210 B | 26-06-1978 |
| | | SE 7412044 A | 27-03-1975 |
| | | US 3979520 A | 07-09-1976 |
| | | ZA 7405967 A | 26-11-1975 |

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82